REMARKS

Applicant respectfully requests reconsideration of the application in view of the foregoing amendments, the following remarks, and the accompanying Rule 132 Declaration of Dr. Dana Hilt.

I. **Claim Amendments**

Claim 3 is amended to more clearly recite what Applicant regards as their invention with respect to the recited embodiment. Support for the amended claim is found, for example, in paragraph [0013] of the specification as filed.

Upon entry of the amendment, claims 1-4 and 6-14 will remain pending.

II. **IDS – September 17, 2007 Telephone Interview**

The Examiner crossed off several foreign language references (G1-G3) from the lists of references submitted by Applicant. Applicant previously submitted an additional Information Disclosure Statement to obtain consideration of these references. As reflected in the Interview Summary mailed October 9, 2007, a telephone interview regarding this issue was conducted on September 17, 2007. The substance of the interview was that the Examiner agreed that Applicant had explained the relevance of the foreign language documents and indicated that they would be considered. An initialed copy of the SB-08 was provided with the Interview Summary indicating that all references were considered. Accordingly, it is believed that this issue has been resolved.

III. **November 14, 2007 Office Interview**

Applicant thanks Examiners Ramachandran and Padmanabhan for the courtesies extended to Applicant's representatives during the Office Interview conducted on November 14, 2007. As set forth in the Interview Summary, Applicant discussed the prior art rejections and possible obviousness-type double patenting issues during the interview. The substance of the interview was that the prior art use of tamoxifen to treat mastalgia does not render obvious the use of 4OHT to treat mastalgia. This issue is discussed in more detail below.

IV. The August 23, 2007 Office Action

The Office Action rejects the claims for alleged obviousness for the reasons set forth at pages 2-12 of the Office Action. The gist of the rejections is that it would have been obvious to use 4-OHT in place of tamoxifen to treat mastalgia, and that the skilled artisan would have been motivated to make such a replacement and would have had a reasonable expectation of success in doing so. Applicant respectfully traverses.

A. *The Hilt Declaration Evidences Non-Obviousness*

The accompanying Rule 132 Declaration of Dr. Hilt explains and develops the issues discussed during the November 14, 2007, Office Interview, providing further evidence of the unpredictability in this field and demonstrating that it was not obvious to use 4-OHT to treat mastalgia.

1. Tamoxifen is not a "pro-drug" of 4-OHT

At the outset, Dr. Hilt emphasizes that "it must be understood that tamoxifen is in no way a 'pro-drug' of 4-OHT." Hilt Declaration, ¶9. "Tamoxifen is metabolized into a number of different metabolites, several of which have been shown to be biologically active." Hilt Declaration, ¶9. Dr. Hilt's Declaration shows that, as currently understood, tamoxifen is metabolized into three primary metabolites, which are further metabolized into four secondary metabolites. Hilt Declaration, ¶9. 4-OHT is one of the three primary metabolites, and is not even the major primary metabolite. Instead, it is N-desmethyltamoxifen that is the major primary metabolite. Hilt Declaration, ¶9. N-desmethyltamoxifen is metabolized into three different secondary metabolites, only one of which also is a secondary metabolite of 4-OHT.

Another difference between tamoxifen and 4-OHT discussed by Dr. Hilt relates to estrogen receptor binding affinity. While "tamoxifen has about the same relative binding affinity for the alpha (7) and beta (6) estrogen receptors, 4-OHT has a higher relative binding affinity for the beta estrogen receptor (339) than the alpha estrogen receptor (178)." Hilt

Declaration, ¶10. Thus, someone skilled in the art would not expect 4-OHT to be biologically equivalent to tamoxifen.

When the 4-OHT comprises a blend of *E* and *Z* isomers, as recited in claim 3, additional differences arise. As explained by Dr. Hilt, the commercially available form of tamoxifen is *trans (Z)* tamoxifen, which "metabolizes into the *Z* isomer of 4-OHT only." Hilt Declaration, ¶10. Dr. Hilt notes that if the relevant activity of tamoxifen were associated with only the *Z* isomer of 4-OHT—the only isomer formed *in vivo* from tamoxifen metabolization— then "administering a blend of *E* and *Z* isomers would be expected to result in reduced efficacy, due to a smaller amount of active species being administered." Hilt Declaration, ¶10. This difference is significant because the *Z* and *E* isomers have different activities. The *Z* isomer of 4-OHT has anti-estrogenic activity, while the *E* isomer is a true selective estrogen receptor modulator (SERM) that exhibits both pro- and anti-estrogenic activity. Hilt Declaration, ¶10. Thus, as Dr. Hilt states, "administering a blend of the *Z* and *E* isomers of 4-OHT instead of tamoxifen may result in estrogenic activity where only anti-estrogenic activity is desired." Hilt Declaration, ¶10.

For at least these reasons, those skilled in the art understood at the time of the invention that administering 4-OHT would not be equivalent to administering tamoxifen.

2. SERM Activity Is Very Unpredictable

The obviousness rejections are based at least in part on the assumption that the known activity of 4-OHT, *e.g.*, its estrogen receptor binding activity, is predictive of usefulness in any therapy in which tamoxifen is useful, including the treatment of mastalgia. As Dr. Hilt explains in his declaration, SERM activity is not so predictable.

First, it must be recognized that "tamoxifen has many activities other than its anti-estrogen activity," as Dr. Hilt points out. Hilt Declaration, ¶12. For example, "[t]amoxifen can behave either as a frank estrogen (pure agonist), a partial agonist or as an antagonist, depending on the species, target organs, and end-points assessed." Hilt Declaration, ¶12 (quoting Lonning *et al.*, *Clin. Pharmacokinet.* 22: 327-58, 331 (1992) (copy attached to Hilt Declaration). Dr. Hilt also notes other proposed mechanisms of tamoxifen action that include

"inhibit[ing] the conversion of estrone sulfate to estradiol, bind[ing] to 'antiestrogen binding sites,' and inhibit[ing] protein kinase C or calmodulin." *Id.*

Given the various activities of tamoxifen, it may not be surprising that "[d]ifferent tamoxifen metabolites have different activities." Hilt Declaration, ¶15. As noted in the Office Action, and confirmed in the literature cited by Dr. Hilt, "4-OHT has a strong binding affinity for the estrogen receptor and exhibits anti-estrogen activity *in vivo* in humans." Hilt Declaration, ¶15. "In contrast, dihydroxytamoxifen has an estrogen receptor binding affinity that is similar to estradiol, and is a 'partial agonist with anti-estrogenic properties' in a murine uterine weight test, 'although both tamoxifen and dihydroxytamoxifen are full estrogen agonists in the mouse.'" Hilt Declaration, ¶15 (quoting Jordan *et al.*, *Breast Cancer Res. & Treat.* 2: 123-38, 131 (1982) (copy attached to Hilt Declaration). Another metabolite, Metabolite E, "appears to be a 'weak estrogen' in the immature rat uterine weight test, while Metabolite Y 'is a weak antiestrogen with partial estrogenic activity in the rat uterus.'" *Id.*

As explained by Dr. Hilt, "because tamoxifen has a number of biologic activities, and a number of biologically active metabolites, *a priori* predicting which specific activity and metabolite of tamoxifen might be useful for the treatment of any breast condition is not an undertaking that can be carried out with any reasonable level of certainty." Hilt Declaration, ¶13. Dr. Hilt attests that, prior to the work of Applicant, "it was not known that the anti-estrogen activity associated with . . . 4-OHT . . . is a relevant activity for treating mastalgia." Hilt Declaration, ¶12.

3. Anti-Estrogen Activity Does Not Predict Clinical Efficacy

While the Examiners have focused on the anti-estrogen activity of 4-OHT, Dr. Hilt explains "that anti-estrogen activity does not always correlate with pharmacological efficacy." Hilt Declaration, ¶19. Indeed, "an anti-estrogen agent that is effective for treating one condition may not be effective for treating another condition." Hilt Declaration, ¶19. Dr. Hilt discusses this point with reference to Gradishar & Jordan, *J. Clin. Oncol.* 15: 840-52 (1997) (copy attached to the Hilt Declaration). Those authors state plainly at page 841 that "[r]eceptor binding and biologic activity are now viewed as two separate functions."

As recounted by Dr. Hilt, "[t]he story of droloxifene taught those working in the field that estrogen receptor binding activity is not necessarily predictive of biological activity." Hilt Declaration, ¶20. "By 1994, this tamoxifen metabolite was proving to be a promising candidate for breast cancer therapy." Hilt Declaration, ¶20. "Droloxifene binds the estrogen receptor with 10-60 times the affinity of tamoxifen, and was found to be safer than tamoxifen in animal studies." Hilt Declaration, ¶20. Indeed, Gradishar & Jordan, *supra*, at page 841, characterized droloxifene as reflecting "[t]he principle of an antiestrogen with high affinity for the [estrogen receptor]."

The droloxifene story did not end well, however. As Dr. Hilt recounts, "by 1998, it was reported that 'interim data from a phase III trial was discouraging, showing that droloxifene offered no benefit beyond [tamoxifen].'" Hilt Declaration, ¶20 (quoting McNeil, *J. Nat'l Cancer Inst.* 90: 956-57, 957 (1998) (copy attached to Hilt Declaration) (internal quotations omitted). "In 2002, the investigators published the results of that trial, which was halted early, concluding that '[d]roloxifene was significantly less effective than tamoxifen overall.'" Hilt Declaration, ¶20 (quoting Buzdar *et al.*, *Breast Cancer Res. & Treat.* 73: 161-75, 161 (2002) (copy attached to Hilt Declaraton). The whole droloxifine project was dropped. Hilt Declaration, ¶20.

Thus, by the time of the invention, those skilled in the art were aware that "identifying a high affinity anti-estrogenic metabolite of tamoxifen does not predict in any way utility, let alone a specific 'anti-estrogenic' clinically beneficial effect in a specific patient population." Hilt Declaration, ¶20. Thus, the skilled artisan could not have reasonably predicted from the known estrogen receptor binding activity of 4-OHT that 4-OHT could be used to treat mastalgia.

Dr. Hilt discusses yet another example of the high level of unpredictability in this field—raloxifene. As explained by Dr. Hilt, "[r]aloxifene is a selective estrogen receptor modulator with anti-estrogen activity." Hilt Declaration, ¶21. Raloxifene "has a similar activity as tamoxifen in treating breast cancer in menopausal women, but is reported to have mixed effects on breast density." Hilt Declaration, ¶21. For example, Dr. Hilt cites Freedman *et al.*, *J. Nat'l Cancer Inst.* 93: 51-56 (2001) (copy attached to Hilt Declaration), as

presenting data indicating that raloxifene "did not increase breast density," but achieved only a 1.5% or 1.7% (depending on the dose) decrease in breast density, where the placebo achieved a 1.3% decrease. On the other hand, Dr. Hilt cites Christodoulakos *et al.*, *Menopause* 9: 110-16 (2002) (abstract attached to Hilt Declaration), which reports on a study "where 6.3% of patients treated with raloxifene showed an increase in breast density, where no increase was seen in the control group." Hilt Declaration, ¶21. The story of raloxifene shows that even proven efficacy in one anti-estrogen context, *e.g.*, treatment of breast cancer, is not predictive of efficacy in another anti-estrogen context, *e.g.*, reduction of breast density.

Thus, as attested by Dr. Hilt, "those working in the field knew by 1998 (well before the patent applications were filed) that estrogen receptor binding activity was not necessarily predictive of clinical efficacy." Hilt Declaration, ¶22.

4. Other Active Metabolites of Tamoxifen Were Known

During the Office Interview, the Examiners asked whether the biological activity of other tamoxifen metabolites was known at the time of the invention. Dr. Hilt's Declaration discusses the state of the art with respect to tamoxifen metabolites, and provides evidence that other (perhaps more promising) metabolites were known in the art by the time of the invention.

As summarized by Dr. Hilt, "before the December 2002 priority date of the applications, a number of tamoxifen metabolites had been discovered and studied, several of which had raised interest as pharmacologically active metabolites that might be useful, for example, for treating breast cancer." Hilt Declaration, ¶14. For example, Dr. Hilt cites Jordan *et al.*, *Breast Cancer Res. & Treat.* 2: 123-38 (1982) (copy attached to Hilt Declaration), for providing a review of tamoxifen metabolites, including Metabolite A, Metabolite B (4-OHT), Metabolite D (catechol/dihydroxytamoxifen), Metabolite E, Metabolite F, Metabolite Y, N-desmethyl-tamoxifen and tamoxifen N-oxide. Hilt Declaration, ¶14. Dr. Hilt notes that "[m]any of these metabolites have significant anti-estrogen activities and inhibit estrogen signal transduction." Hilt Declaration, ¶14.

Dr. Hilt attests that "the multiplicity of biologic activities and active metabolites makes the prediction that 4-OHT would be either the optimal choice or even an obvious choice uncertain." Hilt Declaration, ¶14. To the contrary, Dr. Hilt notes that "endoxifen might have been considered to be the 'optimal' alternative to tamoxifen," Hilt Declaration, ¶17, for reasons explained in more detail below.

Endoxifen is also known as 4-hydroxy-N-desmethyltamoxifen. As noted by Dr. Hilt, "[b]y 1982, endoxifen had been discovered and reported to have an estrogen receptor binding affinity many times greater than tamoxifen." Hilt Declaration, ¶16. For example, Dr. Hilt cites data reported in Robertson *et al.*, *supra*, showing "endoxifen to have a relative binding affinity for the rat uterine estrogen receptor of 143, as compared to a relative binding affinity of 2 for *trans (Z)* tamoxifen." Dr. Hilt recounts that, by 1990, it had been reported that "serum concentrations of endoxifen are generally higher than 4-OHT." Hilt Declaration, ¶17. By 1992, "endoxifen was being studied as having 'biological importance, with an affinity for the estrogen receptor several-fold higher than that of *trans*-tamoxifen.'" Hilt Declaration, ¶17 (quoting Lonning, *supra*, at 335). Indeed, endoxifen is still being studied as an important metabolite of tamoxifen in the treatment of breast cancer. *See, e.g.,* Jordan, *Steroids* 72: 829-42 (Abstract attached) ("Recent studies have identified . . . endoxifen as an important metabolite of tamoxifen necessary for antitumor actions.").

Accordingly, as attested by Dr. Hilt, "by the 2002 priority date of the applications, 4-OHT was not the only active metabolite of tamoxifen with promise for pharmacological activity and was not necessarily the most promising or viable choice for further study." Hilt Declaration, ¶18.

5. Pre- Versus Post-Menopausal Patients

The only 4-OHT efficacy data in the references cited in the Office Action come from studies in post-menopausal patients, *i.e.*, the post-menopausal breast cancer patients in the Pujol study. The present invention relates to the treatment of mastalgia, however, which is a condition that arises in pre-menopausal patients. Hilt Declaration, ¶23. As Dr. Hilt explains, it is "important to keep in mind that tamoxifen and other SERMs and anti-estrogen agents can

have different activities in pre-menopausal women than in post-menopausal women, who lack the ability to produce endogenous estrogen." Hilt Declaration, ¶23. Thus, Dr. Hilt attests, "results obtained in post-menopausal women are not predictive of results that will be obtained in pre-menopausal women, who might increase production of endogenous estrogen in response to . . . anti-estrogen activity." Hilt Declaration, ¶23. Those skilled in the art therefore would not understand the data reported in Pujol to be predictive of results in pre-menopausal patients, such as mastalgia patients.

6. 4-OHT Efficacy Against Mastalgia Was Not Predictable

In summary, Dr. Hilt's Declaration evidences that by 2002, "those working in the field knew that selective estrogen receptor modulators were highly unpredictable, can have different (even opposite) activities in different tissues, and can have different effects in pre- vs. post menopausal women." Hilt Declaration, ¶24. For at least these reasons, "it was not possible to predict from studies with tamoxifen, or from studies of 4-OHT in different patient populations, that 4-OHT could be used to treat mastalgia." Hilt Declaration, ¶24.

B. *The Obviousness Rejections*

Applicant turns now to the specific rejections raised in the Action.

1. Claims 1-3, 6-8, 10 and 11-14

Claims 1-3, 6-8, 10 and 11-14 are rejected for alleged obviousness in view of (i) Mauvais-Jarvis, *Curr. Ther. Endocrin. Metab.* 280-84 (1988), Pujol *et al.*, *Cancer Chemother. Pharmacol.* 36: 493-98 (1995) and Fentiman *et al.*, *Br. J. Surg.* 75: 845-46 (1988) ; (ii) Mauvais-Jarvis, Senologie & Pathologie Mammaire, 4eme Cong. Int'l, 128-32 (1986), Pujol and Fentiman and (iii) Pujol and Fentiman. None of these combinations of references render obvious the present invention, however.

As set forth at pages 5 and 7 of the Action, the crux of rejections (i) and (ii) is that "[i]t would have been obvious to one of ordinary skill in the art to use [4-OHT] for tamoxifen in the treatment of cyclical breast pain as [Mauvais-]Jarvis teaches the drawbacks of using tamoxifen and the advantages of [4-OHT] and it is well known in the art that [4-OHT] is an

active metabolite of tamoxifen." As set forth at page 8 of the Action, the crux of rejection (iii) is that Pujol provides motivation to use 4-OHT to treat mastalgia by its teachings that 4-OHT "is an active metabolite of tamoxifen," has "100-1000 fold stronger affinity to estrogen receptors" than tamoxifen, and is "one of the most potent anti-estrogens." While these statements may seem logical in hindsight, Dr. Hilt's Declaration evidences that, at the time of the invention, the replacement of tamoxifen with 4-OHT was neither an obvious choice nor a predictable undertaking. Instead, those skilled in the art understood that the clinical activity of selective estrogen receptor modulators (SERMs) such as 4-OHT was highly unpredictable and variable from tissue type to tissue type, patient population to patient population (particularly pre- versus post-menopausal patients), and condition to condition. Thus, prior to the present invention, the skilled artisan had no reasonable basis to expect that 4-OHT could be used successfully in place of tamoxifen to treat mastalgia.

There are several additional reasons why the Pujol reference does not support the obviousness rejection. First, as noted above, Pujol reports results obtained in post-menopausal cancer patients, while the present invention relates to the treatment of mastalgia, a condition that arises in pre-menopausal patients. As explained above and in the Hilt Declaration, "results obtained in post-menopausal women are not predictive of results that will be obtained in pre-menopausal women, who might increase production of endogenous estrogen in response to . . . anti-estrogen activity." Hilt Declaration, ¶23.

Moreover, while the Office Action (at page 3) characterizes Pujol as teaching "percutaneous administration of . . . [4-OHT] in a hydroalcoholic get to breast areas for the treatment of breast cancer," that characterization is misleading. As Dr. Hilt explains, "Pujol reports a Phase I study that measured the concentration of 4-OHT in the breast tissue of breast cancer patients after percutaneous administration of a 4-OHT hydroalcoholic gel." Hilt Declaration, ¶26. "The authors found a lower breast tissue concentration as compared to oral tamoxifen and concluded that 'at the doses described in this study, percutaneous 4-OH-TAM ***cannot be proposed as an alternative tamoxifen treatment.***'" Hilt Declaration, ¶26 (quoting the Pujol abstract). Thus, as Dr. Hilt attests, "this Pujol reference does not suggest that percutaneous 4-OHT can be successfully used in place of oral tamoxifen to treat breast cancer, let alone to treat mastalgia."

The cited Mauvais-Jarvis references also do not support obviousness, because they fail to provide any reasonable expectation of success. As explained by Dr. Hilt, the Mauvais-Jarvis, *Curr. Ther. Endocrin. Metab.* 280-84 (1988), reference makes statements regarding the potential efficacy of percutaneous 4-OHT, but those statements "are entirely speculative," and not based supporting clinical data. Hilt Declaration, ¶27. "The only data cited pertain to studies showing that when 4-OHT is topically applied to the breast it is 'absorbed through the skin and is predominantly concentrated into subcellular fractions of breast tissue.'" Hilt Declaration, ¶27. Dr. Hilt emphasizes that "[n]o efficacy experiments support the hypothesis that percutaneous 4-OHT could be useful against benign breast disease." Hilt Declaration, ¶27. Indeed, the page of Mauvais-Jarvis cited in the Office Action states that "[t]his possible therapeutic approach is under investigation and is not yet available." The other cited Mauvais-Jarvis reference, Mauvais-Jarvis, SENOLOGIE & PATHOLOGIE MAMMAIRE, 4eme Cong. Int'l, 128-32 (1986), suffers from similar shortcomings. Dr. Hilt explains that its statements of efficacy are "entirely speculative, and based only on phase I data showing that topically applied 4-OHT localizes in subcellular breast tissue." Hilt Declaration, ¶28. Thus, Dr. Hilt attests that, contrary to the position set forth in the Office Action, these Mauvais-Jarvis references do "not provide the person skilled in the field with a sufficient scientific basis to reasonably predict that 4-OHT could be used to treat mastalgia," Hilt Declaration, ¶27, 28. This is particularly true in view of the high level of unpredictability in the field, as discussed above.

2. Claim 9

Claim 9 is rejected for alleged obviousness in view of Fentiman, Pujol and Kochinke, U.S. Patent 5,613,958. This combination of references, however, fails to suggest the invention recited in claim 9, which is directed to embodiments where the 4-hydroxy tamoxifen is provided in a hydroalcoholic gel that comprises ethyl alcohol, isopropyl myristate, and hydroxypropylcellulose.

The inability of Fentiman and Pujol to teach the method recited in independent claim 1 is demonstrated above. Kochinke is cited for teaching transdermal systems that may comprise isopropyl myristate, ethanol and hydroxypropylcellulose. These teachings,

however, do not remedy the inability of Fentiman and Pujol to teach the method recited in claim 1. Moreover, Kochinke is directed to a multi-layer transdermal patch, and thus has little relevance to the hydroalcoholic gel recited in claim 9. Thus, the obviousness rejection of claim 9 is improper, and should be withdrawn.

Claim 4

Claim 4 is rejected for alleged obviousness in view of Fentiman, Pujol and Mauvais-Jarvis *et al.*, *Cancer Res.* 46: 1521-25 (1986) or Malet et al., *Cancer Res.* 48: 7193-99 (1988). This combination of references, however, fails to suggest the invention recited in claim 4, which is directed to embodiments where the 4-hydroxy tamoxifen is a *trans* isomer.

The inability of Fentiman and Pujol to teach the method recited in independent claim 1 is demonstrated above. Mauvais-Jarvis is cited for teaching that the *trans* isomer of 4-hydroxy tamoxifen is a "very active metabolite of tamoxifen," and Malet reports that both the *trans* and *cis* isomers of 4-hydroxy tamoxifen were active to inhibit breast cell division. These teachings, however, do not remedy the inability of Fentiman and Pujol to teach the method recited in claim 1. Thus, the obviousness rejection of claim 4 is improper, and should be withdrawn.

C. ***Obviousness-Type Double Patenting***

As noted above, during the Office Interview the Examiners raised the possibility of there being an obviousness-type double patenting issue with respect to the claims of co-pending application 10/734,638. Without acquiescing on the merits, Applicant submits herewith a terminal disclaimer to obviate any issue of obviousness-type double patenting.

Conclusion

Applicant believes that the application is now in condition for allowance, and an early notice to that effect is earnestly solicited.

Should there be any questions regarding this application, or should any issue remain, the Examiner is invited to contact the undersigned by telephone in order to advance prosecution.

The Commissioner is hereby authorized to charge any additional fees which may be required regarding this application under 37 C.F.R. §§ 1.16-1.17, or credit any overpayment, to Deposit Account No. 19-0741. Should no proper payment be enclosed herewith, as by a check or credit card payment form being in the wrong amount, unsigned, post-dated, otherwise improper or informal or even entirely missing, the Commissioner is authorized to charge the unpaid amount to Deposit Account No. 19-0741. If any extensions of time are needed for timely acceptance of papers submitted herewith, Applicant hereby petitions for such extension under 37 C.F.R. §1.136 and authorizes payment of any such extensions fees to Deposit Account No. 19-0741.

Respectfully submitted,

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1: Steroids. 2007 Nov;72(13):829-42. Epub 2007 Jul 27.

New insights into the metabolism of tamoxifen and its role in the treatment and prevention of breast cancer.

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The metabolism of tamoxifen is being redefined in the light of several important pharmacological observations. Recent studies have identified 4-hydroxy N-desmethyltamoxifen (endoxifen) as an important metabolite of tamoxifen necessary for antitumor actions. The metabolite is formed through the enzymatic product of CYP2D6 which also interacts with specific selective serotonin reuptake inhibitors (SSRIs) used to prevent the hot flashes observed in up to 45% of patients taking tamoxifen. Additionally, the finding that enzyme variants of CYP2D6 do not promote the metabolism of tamoxifen to endoxifen means that significant numbers of women might not receive optimal benefit from tamoxifen treatment. Clearly these are particularly important issues not only for breast cancer treatment but also for selecting premenopausal women, at high risk for breast cancer, as candidates for chemoprevention using tamoxifen.

PMID: 17765940 [PubMed - indexed for MEDLINE]

Related Links

- Active tamoxifen metabolite plasma concentrations after coadministration of tamoxifen and the selective serotonin reuptake inhibitor [J Natl Cancer Inst. 2003]
- CYP2D6 genotype, antidepressant use, and tamoxifen metabolism during adjuvant breast [J Natl Cancer Inst. 2005]
- Quantitative effect of CYP2D6 genotype and inhibitors on tamoxifen metabolism: implication for optimization of breast cancer treatment [Clin Pharmacol Ther. 2006]